BMJ Oncology

SAFFRON-301: a randomised phase III study of sitravatinib in combination with tislelizumab in patients with locally advanced or metastatic non-small cell lung cancer

Qing Zhou ,[1,2,3] Bo Gao,[4] Jie Hu,[5] Jun Zhao,[6] Mengzhao Wang ,[7] Kai He,[8] Wei Zhang,[9] Chunling Liu,[10] Jian Fang ,[6] Xing ya Li,[11] Zhehai Wang,[12] Marco Matos,[13] Vineet Kwatra,[14] Wenjuan Zheng,[15] Chenyang Wang,[15] Yaxi Chen,[16] Juan Zhang,[15] Jun Wang,[15] Yi-Long Wu [2,3,17]

To cite: Zhou Q, Gao B, Hu J, *et al*. SAFFRON-301: a randomised phase III study of sitravatinib in combination with tislelizumab in patients with locally advanced or metastatic non-small cell lung cancer. *BMJ Oncology* 2026;**5**:e000890. doi:10.1136/bmjonc-2025-000890

Received 11 July 2025
Accepted 22 January 2026

Linked

► https://doi.org/10.1136/bmjonc-2025-001066

Check for updates

© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to
Dr Yi-Long Wu; syylwu@live.cn

ABSTRACT

Background Many patients with non-small cell lung cancer (NSCLC) have tumours that are either refractory or develop resistance following an initial response to anti-programmed cell death protein (ligand)-1 (PD-(L)1)-based treatment, resulting in limited treatment options. SAFFRON-301 evaluated whether combining the multikinase inhibitor, sitravatinib, with the anti-PD-1 antibody, tislelizumab, may overcome resistance to anti-PD-(L)1 therapy.

Methods SAFFRON-301 (NCT04921358) was an open-label, randomised, phase III trial enrolling patients with unresectable locally advanced/metastatic NSCLC, who had disease progression on or after platinum-based chemotherapy and anti-PD-(L)1 antibodies. No more than two lines of prior systemic therapy were allowed. Patients were randomised 1:1 to receive sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks or docetaxel 75 mg/m^2 intravenously every 3 weeks. Dual primary endpoints were overall survival (OS) and Independent Review Committee (IRC)-assessed progression-free survival (PFS).

Results Overall, 377 patients were enrolled and randomised to receive sitravatinib plus tislelizumab (n=187) or docetaxel (n=190); 51.2% had squamous histology and 36.6% had PD-L1 expression in ≥1% of tumour cells. At a median follow-up of 11.7 (sitravatinib plus tislelizumab) and 11.4 months (docetaxel), median OS was similar (11.5 (95% CI 9.4 to 14.6) vs 11.4 (9.9 to 15.0) months, respectively; HR, 1.02 (95% CI 0.75 to 1.39)) between treatment arms. IRC-assessed median PFS was numerically longer with sitravatinib plus tislelizumab (4.4 (95% CI 4.0 to 5.7) months) vs docetaxel (2.9 (95% CI 2.6 to 4.2) months); HR, 0.82 (95% CI 0.62 to 1.07). IRC-assessed overall response rate was 12.3% with sitravatinib plus tislelizumab vs 12.6% with docetaxel. The most commonly reported treatment-emergent adverse events grade ≥3 in sitravatinib plus tislelizumab arm were hypertension (13.4%), pneumonia (9.1%), palmar-plantar erythrodysesthesia syndrome (6.5%) vs white blood cell count decreased (29.4%), neutrophil count decreased (28.8%), pneumonia (8.5%) and neutropenia (7.3%) in docetaxel arm. Grade 5 haemoptysis occurred in 3 (1.6%) patients with sitravatinib plus tislelizumab. The study was terminated due to an unfavourable risk–benefit analysis.

Conclusions The SAFFRON-301 study was terminated early due to unfavourable risk–benefit assessment in the investigational arm. Due to immature survival data, efficacy results should be interpreted with caution.

Trial registration number NCT04921358.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the phase Ib SAFFRON-103 trial, combination therapy with the multityrosine kinase inhibitor, sitravatinib, plus the anti-programmed cell death protein-1 (anti-PD-1) antibody, tislelizumab, had promising antitumour activity with no new safety signals in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who progressed after anti-PD-1/anti-programmed death-ligand 1 (PD-L1) therapy. The phase III SAFFRON-301 trial was performed to confirm the efficacy signals observed with sitravatinib plus tislelizumab in SAFFRON-103.

WHAT THIS STUDY ADDS

⇒ Combination therapy with sitravatinib plus tislelizumab had an unclear efficacy benefit with an increased risk of serious and fatal pulmonary haemorrhage in patients with squamous and non-squamous NSCLC who progressed on or after anti-PD-(L)1 therapy and platinum-based chemotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Continued investigation of combination therapy with sitravatinib plus tislelizumab in patients with NSCLC is not warranted.

INTRODUCTION

Checkpoint inhibitor-based immunotherapy that targets the anti-programmed cell death

protein-1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) axis with or without chemotherapy has become a first-line standard-of-care for patients with locally advanced/metastatic non-small cell lung cancer (NSCLC) without actionable genetic alterations.[1–8] Despite initial improvement in some patients, many patients with NSCLC have tumours that are treatment refractory or develop resistance following an initial response to anti-PD-1 or PD-L1-based treatment.[9] Patients with NSCLC without a targetable oncogenic driver who progress during/after platinum-based chemotherapy and anti-PD-(L)1 therapy have limited treatment options; these include (depending on histology) single-agent chemotherapy (docetaxel, pemetrexed, nab-paclitaxel or gemcitabine), or docetaxel in combination with an antiangiogenic agent (nintedanib or ramucirumab).[1 3 10–17] Modest activity combined with tolerability issues creates a substantial unmet need for efficacious and safe treatments for the treatment of second-line and beyond disease in patients with prior exposure to anti-PD-(L)1 agents.[10]

Strategies to improve outcomes and overcome resistance to anti-PD-(L)1 agents are being actively investigated. One rational approach involves combining anti-PD-(L)1 therapy with vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) inhibitors that target the molecular and cellular mechanisms of resistance to anti-PD-(L)1 agents.[9 18 19] VEGF/VEGFR inhibition with both small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs; ie, bevacizumab or ramucirumab) has been studied in combination with anti-PD-(L1) therapy for the treatment of NSCLC.[19] In preclinical models, inhibitors targeting multiple tyrosine kinases, including VEGF (eg, sitravatinib), can stimulate the immune system and stimulate tumour shrinkage.[20]

Early phase clinical trials provided encouraging data supporting the theoretical and preclinical framework for using combination therapy with anti-PD-(L)1 agents plus TKIs or mAbs targeting VEGF and other tyrosine kinases. In a phase Ib/II trial, combination therapy with lenvatinib plus pembrolizumab had promising clinical activity, with an overall response rate (ORR) of 33% at week 24, in patients with histologically and/or cytologically confirmed metastatic NSCLC that progressed after therapy or for which standard therapy was not available.[21] In the phase II COSMIC-021 study, treatment with cabozantinib in combination with atezolizumab was associated with improved clinical outcomes (ORR, 19%) compared with cabozantinib alone (ORR, 6%) in patients with non-squamous stage IV NSCLC who progressed on prior anti-PD-(L)1-based therapy.[22] A randomised phase II trial of ramucirumab and pembrolizumab versus standard-of-care in patients with squamous and non-squamous NSCLC previously treated with immunotherapy met its primary endpoint of improved overall survival (OS) in the ramucirumab and pembrolizumab arm.[23] These encouraging early phase trials justified the performance of phase III trials investigating the same combination therapies in patients with NSCLC previously exposed to anti–PD-(L)1 agents. These phase III trials include LEAP-008 (pembrolizumab plus lenvatinib vs docetaxel), CONTACT01 (cabozantinib plus atezolizumab vs docetaxel) and Pragmatica-Lung (ramucirumab plus pembrolizumab vs standard-of-care).[24–26]

Sitravatinib (MGCD516) is an oral spectrum-selective receptor TKI that targets TAM receptors (TYRO3/AXL/MERTK) and split tyrosine kinase domain-containing receptors (VEGFR2/KIT).[27 28] TAM receptor tyrosine kinases, primarily found on antigen-presenting cells like macrophages, help maintain immune homeostasis by suppressing inflammation.[29] Their overexpression is associated with tumour metastasis, including in lung cancer. Targeting TAM receptors encourages M1 macrophage polarisation and promotes an antitumour immune microenvironment.[20] In addition, targeting VEGFR2 and KIT reduces regulatory T cells and myeloid-derived suppressor cells, lessening immunosuppression and enhancing the effectiveness of PD-(L)1 inhibitors.[30 31] Tislelizumab is an anti-PD-1 humanised monoclonal antibody that binds to PD-1 with high affinity and was designed to minimise binding of fragment crystallisable region receptors on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy.[32 33] By binding to PD-1, tislelizumab prevents PD-1 from interacting with its ligands, PD-L1 and PD-L2.[32] Combination therapy with sitravatinib and tislelizumab was tested in the phase Ib SAFFRON-103 trial which enrolled patients with various solid tumours.[34] Sitravatinib plus tislelizumab had promising antitumour activity in patients with metastatic non-squamous/squamous NSCLC who were refractory/resistant to anti-PD-(L)1 therapy; the mOS was 10.1 and 10.5 months in patients with non-squamous and squamous histology, respectively.[34] The phase III SAFFRON-301 study was therefore initiated to confirm the efficacy signal observed in SAFFRON-103.

Here, we report the results of SAFFRON-301 (ClinicalTrials.gov, NCT04921358), an open-label randomised phase III study of sitravatinib in combination with tislelizumab versus chemotherapy in patients with locally advanced/metastatic NSCLC that progressed on or after platinum-based chemotherapy and anti-PD-(L)1 therapy.

METHODS

Study design and participants

SAFFRON-301 was an open-label, randomised, multicentre, phase III clinical trial (online supplemental files 2–5). Eligible patients had histologically or cytologically confirmed locally advanced or metastatic (stage IIIB/IIIC or stage IV) NSCLC and disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after platinum-based chemotherapy (online supplemental figure 1). Other eligibility criteria included two or fewer lines of prior systemic therapy for locally advanced and

unresectable or metastatic disease, at least one measurable lesion per Response Evaluation in Solid Tumours (RECIST) V.1.1,[35] and Eastern Cooperative Oncology Group performance status of ≤1. Patients with known *EGFR*-sensitising or *BRAF*-sensitising mutation, or *ALK* or *ROS1* rearrangement, squamous NSCLC with central cavitation, or NSCLC with haemoptysis (>50 mL/day), or with radiologic evidence of tumours invading or abutting major blood vessels were ineligible for the study. Detailed inclusion/exclusion criteria are shown in the online supplemental file.

Randomisation and masking

After obtaining informed consent, study personnel accessed the Interactive Response Technology system to randomise treatment assignment (1:1). Patients were stratified by histological subtype (non-squamous vs squamous), PD-L1 expression (<1% tumour cell (TC) vs ≥1% TC; patients whose tissues were unevaluable for PD-L1 expression were included in the <1% TC group) and race (Asian vs non-Asian). PD-L1 expression was determined by the Ventana SP263 assay (Roche Diagnostics, North America).

Treatment and assessments

Patients received sitravatinib 100 mg orally once a day in combination with tislelizumab 200 mg intravenously once every 3 weeks or docetaxel 75 mg/m^2 intravenous once every 3 weeks. Cycles were 21±3 days unless a delay was medically necessary. Tumour assessments were conducted by CT and/or MRI every 6 weeks (±7 days) from cycle 1 day 1 in the first 12 months, and at 9-week±7 day intervals thereafter. Tumour assessment and responses were determined by blinded Independent Review Committee (IRC) and investigator using RECIST V.1.1.[35] Patients were treated until disease progression, intolerable toxicity, death or withdrawal of consent, whichever occurred earlier. Crossover to the other treatment group was not permitted. Patients were contacted every 3 months (±14 days) to assess survival during follow-up.

Outcomes

Primary endpoints

The dual primary endpoints were OS (time from randomisation to death from any cause) and IRC-assessed progression-free survival (PFS; time from randomisation to the first occurrence of disease progression as determined by the IRC based on RECIST V.1.1,[35] or death from any cause, whichever occurred first).

Secondary endpoints

Secondary endpoints included investigator-assessed PFS, IRC-assessed ORR (proportion of patients with partial response (PR) or complete response (CR)), duration of response (DoR; time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, or death from any cause, whichever occurred first), and disease control rate (DCR; proportion of patients whose best overall response was CR, PR, or stable disease) as determined based on RECIST V.1.1.[35]

Statistical analysis

The intention-to-treat (ITT) analysis set included all randomised patients, analysed according to their randomised treatment group. The safety analysis set included all patients who received at least one dose of any study drug. We planned for approximately 420 patients to undergo 1:1 randomisation to receive sitravatinib plus tislelizumab or docetaxel alone, as determined based on the primary endpoints of OS and PFS per IRC with type I error allocation (one-sided) of 0.024 and 0.001, respectively. Approximately 289 OS events were planned for the final analysis of OS, to have a power of 85% with an alpha of 0.024 under the HR assumption of 0.7. Subgroup analyses for OS were prespecified in the statistical analysis plan. Approximately 332 PFS events per IRC were expected to occur at the final analysis of PFS, to have a power of 87% with an alpha of 0.001 under the HR assumption of 0.63. One interim analysis was planned to occur when approximately 197 of the targeted 289 OS events (68.0%) were documented in the ITT analysis set. No efficacy interim analysis of PFS was planned; final analysis of PFS was to be performed at the time of the interim analysis of OS. Due to early termination of the study, the preplanned efficacy interim analysis was aborted. Formal hypothesis testing was not performed.

A treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) with an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurred first. Treatment-related treatment-emergent AEs (TRAEs) included TEAEs considered by the investigator to be related to a study drug or with missing assessment of the causal relationship. AEs were classified based on Medical Dictionary for Regulatory Activities Version 25.0 and were graded based on National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0.[36] Immune-mediated AEs (imAEs) were of special interest. Recommendations for diagnostic evaluation and management of imAEs were based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines.[37 38] ImAEs were identified from all AEs with an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of any drug and up to 90 days from the last dose of any drug, regardless of whether the patient started new anticancer therapy.

RESULTS

Patient population

Patients were enrolled at 61 sites in China and Australia. The first patient was dosed on 27 July 2021. Because the study was terminated early, enrolment was not completed, and efficacy data are premature. The last

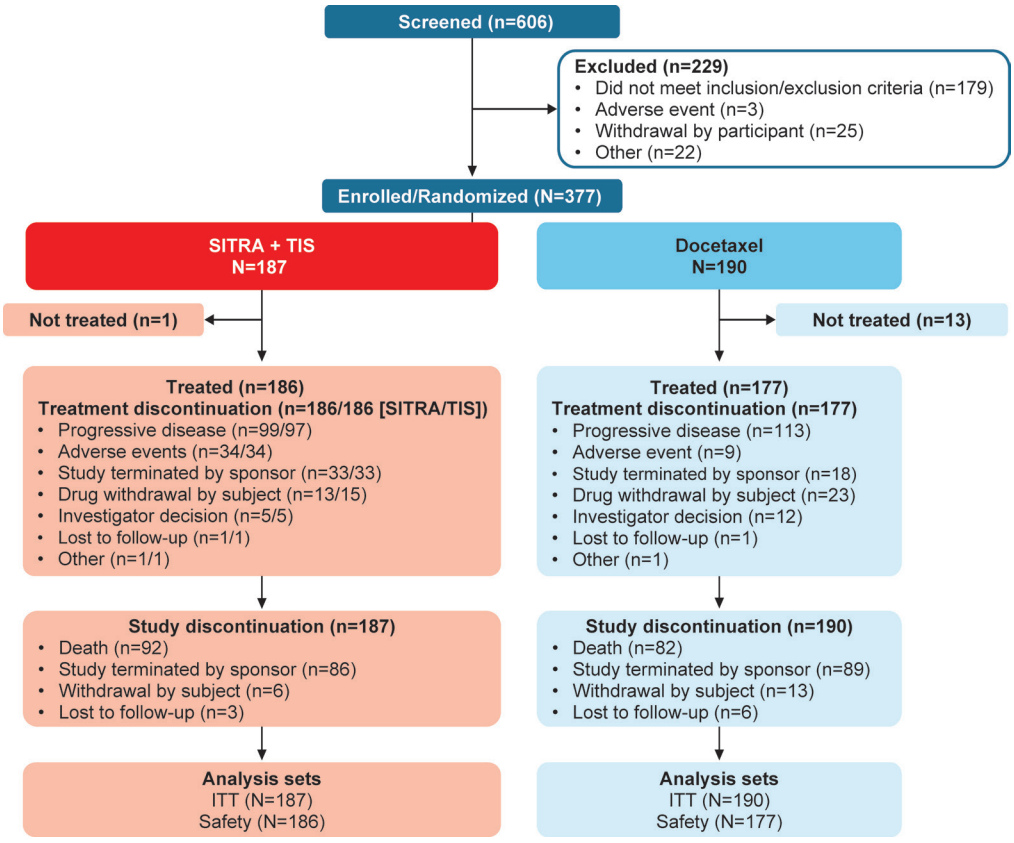


Figure 1 Patient disposition. ITT, intention-to-treat; Sitra, sitravatinib; TIS, tislelizumab.

visit for the last patient was completed on 20 December 2023 (data cut-off).

Overall, 377 patients were randomised (n=187, sitravatinib+tislelizumab; n=190, docetaxel); of these, 14 patients did not receive treatment (1 (0.5%) patient in sitravatinib+tislelizumab arm; 13 (6.8%) patients in docetaxel arm) (figure 1). One patient randomised to sitravatinib+tislelizumab who did not receive treatment had a significant decline in Eastern Cooperative Oncology Group performance status due to increasing pain since screening. Of the 13 patients who did not receive docetaxel, 12 patients withdrew from treatment due to patient decision, and 1 patient was not treated because of difficult venous access; this patient subsequently deteriorated with elevated bilirubin and was then not eligible for study treatment. Median study follow-up time was 8.0 months (range, 0.4–25.3 months) and 7.6 months (range, 0–25.1 months) for sitravatinib+tislelizumab and docetaxel, respectively. By the data cut-off date, all treated patients had discontinued treatment, mostly due to progressive disease; all patients discontinued from the study, mostly due to death or study termination by sponsor (figure 1). Baseline demographics and disease characteristics, including randomisation stratification factors (histological subtype, PD-L1 expression and race), were generally well balanced between arms (table 1).

Efficacy

Primary efficacy endpoints

At data cut-off, the median follow-up time for OS was 11.7 months and 11.4 months in the sitravatinib+tislelizumab and docetaxel arms respectively, with deaths reported in 48.7% and 42.1% of patients, respectively. Median OS was 11.5 months (95% CI 9.4 to 14.6) and 11.4 months (95% CI 9.9 to 15.0) in the sitravatinib+tislelizumab and docetaxel arms, respectively, with no survival benefit (HR 1.02 (95% CI 0.75 to 1.39)) (figure 2A). IRC-assessed PFS was numerically longer in the sitravatinib+tislelizumab compared with the docetaxel arm: 4.4 months (95% CI 4.0 to 5.7) versus 2.9 months (95% CI 2.6 to 4.2; HR 0.82 (95% CI 0.62 to 1.07)) (figure 2B).

Secondary efficacy endpoints

Investigator-assessed median PFS was 4.4 months (95% CI 4.0 to 5.6) and 2.9 months (95% CI 2.6 to 4.1) in the sitravatinib+tislelizumab and docetaxel arms, respectively (HR 0.64 (95% CI 0.50 to 0.83)) (figure 2C). IRC-assessed ORR was similar in both arms (12.3% (95% CI 8.0% to 17.9%) vs 12.6% (95% CI 8.3% to 18.2%) for sitravatinib+tislelizumab and docetaxel, respectively) (table 2). There were no CRs in either group; PR rates were similar in both arms (sitravatinib+tislelizumab, 12.3% vs docetaxel, 12.6%). IRC-assessed DCR was 69.5% (95% CI 62.4% to 76.0%) and 53.7% (46.3% to 60.9%) in the sitravatinib+tislelizumab and

Table 1 Patient demographics and baseline characteristics (ITT population)

	Sitravatinib+tislelizumab (n=187)	Docetaxel (n=190)	Total (N=377)
Age, years			
Median	63.0	63.0	63.0
Min, max	29, 76	34, 79	29, 79
Age group, n (%)			
<65 years	106 (56.7)	112 (58.9)	218 (57.8)
≥65 years	81 (43.3)	78 (41.1)	159 (42.2)
Sex, n (%)			
Male	153 (81.8)	151 (79.5)	304 (80.6)
Female	34 (18.2)	39 (20.5)	73 (19.4)
Race*, n (%)			
Asian	175 (93.6)	177 (93.2)	352 (93.4)
White	12 (6.4)	13 (6.8)	25 (6.6)
ECOG performance status, n (%)			
0	47 (25.1)	46 (24.2)	93 (24.7)
1	140 (74.9)	144 (75.8)	284 (75.3)
Histology*, n (%)			
Squamous	96 (51.3)	97 (51.1)	193 (51.2)
Non-squamous	91 (48.7)	93 (48.9)	184 (48.8)
PD-L1 expression status*, n (%)			
≥1%	68 (36.4)	70 (36.8)	138 (36.6)
<1%	106 (56.7)	107 (56.3)	213 (56.5)
Not evaluable	13 (7.0)	13 (6.8)	26 (6.9)
Smoking status, n (%)			
Current	21 (11.2)	24 (12.6)	45 (11.9)
Former	110 (58.8)	108 (56.8)	218 (57.8)
Never	56 (29.9)	58 (30.5)	114 (30.2)
Number of lines of prior systemic therapy, n (%)			
1	142 (75.9)	140 (73.7)	282 (74.8)
2	45 (24.1)	50 (26.3)	95 (25.2)
Type of last line systemic therapy, n (%)			
Anti–PD-(L)1 monotherapy	8 (4.3)	13 (6.8)	21 (5.6)
Chemotherapy	1 (0.5)	1 (0.5)	2 (0.5)
Anti–PD-(L)1 in combination with chemotherapy	150 (80.2)	156 (82.1)	306 (81.2)
Other†	28 (15.0)	20 (10.5)	48 (12.7)

*Value per EDC.
†Other includes therapies not listed as above, such as anti-VEGF antibody or antiangiogenic therapy in combination with anti–PD-(L)1 and/or chemotherapy.
ECOG, Eastern Cooperative Oncology Group; EDC, electronic data capture; ITT, intention-to-treat; Max, maximum; Min, minimum; PD-L1, programmed cell death protein-ligand1; VEGF, vascular endothelial growth factor.

docetaxel arms, respectively (table 2); IRC-assessed DoR was 6.0 months and not reached in the sitravatinib+tislelizumab therapy and docetaxel arms, respectively (table 2).

Subgroup analyses

Consistent with the overall population analysis, there were no clear improvements in OS favouring sitravatinib+tislelizumab over docetaxel in any prespecified subgroup (online supplemental figure 2A).

In a post hoc subgroup analysis for PFS, the HR with sitravatinib+tislelizumab versus docetaxel numerically favoured investigational arm in patients with squamous histology (HR 0.59 (95% CI 0.40 to 0.88)), in patients aged <65 years (HR 0.66 (95% CI 0.47 to 0.92)), and in multiple other subgroups with specific clinical pathology characteristics (online supplemental figure 2B). However, given the limited number of patients in each subgroup, the results should be interpreted with caution.

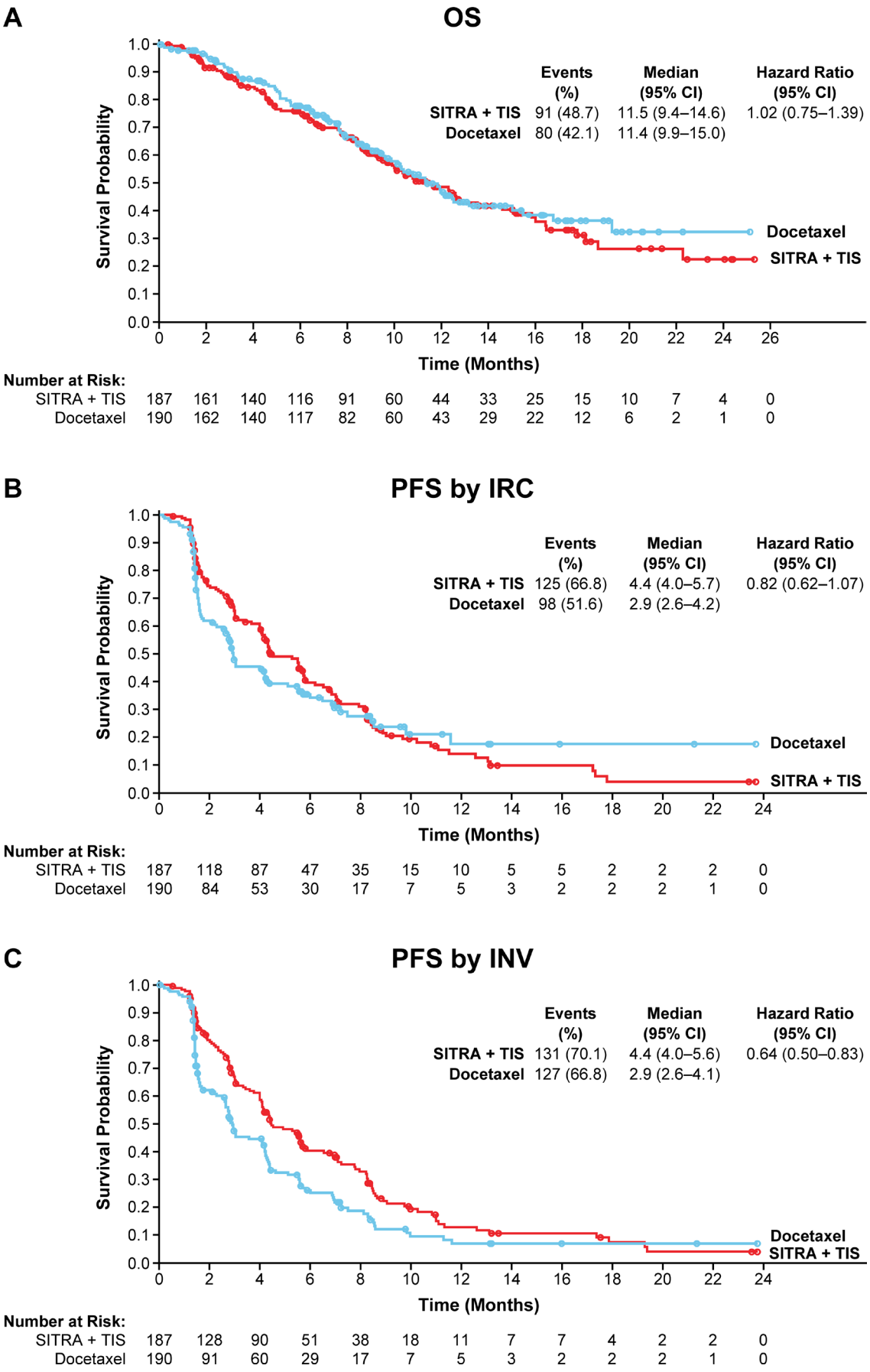


Figure 2 Overall survival (OS) and progression-free survival (PFS). (A) OS. (B) IRC-assessed PFS. (C) Investigator (INV)-Assessed PFS. IRC, Independent Review Committee; SITRA, sitravatinib; TIS, tislelizumab.

Table 2 Disease response by IRC (ITT analysis set)

Response category	Sitravatinib+tislelizumab (n=187)	Docetaxel (n=190)
Best overall response, n (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	23 (12.3)	24 (12.6)
Stable disease	102 (54.5)	74 (38.9)
Non-CR/non-PD	5 (2.7)	4 (2.1)
Progressive disease	33 (17.6)	51 (26.8)
Could not be determined	24 (12.8)	37 (19.5)
Overall response rate, n (%)	23 (12.3)	24 (12.6)
95% CI (%)*	8.0 to 17.9	8.3 to 18.2
Disease control rate	130 (69.5)	102 (53.7)
95% CI (%)*	62.4 to 76.0	46.3 to 60.9
Median duration of response (95% CI), months†	6.0 (3.2, 8.5)	NR (5.4, NE)

Complete response and partial response were confirmed per RECIST V.1.1.
*The 95% CI was estimated using the Clopper-Pearson method.
†Medians were estimated using the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log–log transformation.
CR, complete response; IRC, Independent Review Committee; ITT, intention-to-treat; NE, not estimable; NR, not reached; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours.

Safety

The median duration of exposure was 4.1 months (range, 0.0–24.3) and 4.1 months (range, 0.5–24.8) for sitravatinib and tislelizumab, respectively, with median relative dose intensities of 83.3% (range, 7.7–100.0) and 96.9% (range, 40.0–108.6). Median duration of exposure to docetaxel was 2.1 months (range, 0.1–25.8) with a median relative dose intensity of 95.3% (range, 40.9–103.7).

Overall, 183 (98.4%) and 162 (91.5%) patients in the sitravatinib+tislelizumab and docetaxel arms, respectively, had TEAEs (table 3 and online supplemental table 2). The incidence of grade 3 TEAEs was higher in the sitravatinib+tislelizumab than the docetaxel arm (121 (65.1%) patients vs 100 (56.5%) patients) (table 3 and online supplemental table 2). Grade ≥3 TEAEs occurring in ≥5% of sitravatinib+tislelizumab arm were hypertension (25 (13.4%)), pneumonia (17 (9.1%)), palmar-plantar erythrodysesthesia syndrome (12 (6.5%)), and hypokalaemia (10 (5.4%)) (table 3). Grade ≥3 TEAEs occurring in ≥5% of docetaxel arm were white blood cell count decreased (52 (29.4%)), neutrophil count decreased (51 (28.8%)), pneumonia (15 (8.5%)), neutropenia (13 (5.3%)) and febrile neutropenia (10 (5.6%)) (table 3). An overview of TRAEs and TRAEs by preferred term is shown in online supplemental tables 2 and 3, respectively.

45 (24.2%) and 15 (8.5%) patients in the sitravatinib+tislelizumab and docetaxel arms, respectively, had a TEAE leading to treatment discontinuation (online supplemental table 2). The most common TEAEs leading to discontinuation in the sitravatinib+tislelizumab arm were haemoptysis (4 (2.2%)), fatigue (3 (1.6%)), and immune-related lung disease (3 (1.6%)), whereas those in the docetaxel arm included pneumonitis (2 (1.1%)), cancer pain (2 (1.1%)), peripheral sensory neuropathy (2 (1.1%)) and pleural effusion (2 (1.1%)).

The incidence of any grade (91 (48.9%) vs 18 (10.2%)) and ≥grade 3 (18 (9.7%) vs 4 (2.3%)) imAEs was higher in the sitravatinib+tislelizumab versus docetaxel arm, respectively (online supplemental table 4). The most commonly reported imAEs of any grade by category in the sitravatinib+tislelizumab and docetaxel arms, respectively, were immune-mediated endocrinopathies (hypothyroidism) (47 (25.3%) vs 0%), immune-mediated skin adverse reaction (37 (19.9%) vs 11 (6.2%)), and immune-mediated pneumonitis (pneumonitis and immune-mediated lung disease) (9 (4.8%) vs 4 (2.3%)) (online supplemental table 4). Immune-mediated pneumonitis that was ≥grade 3 occurred in 6 (3.2%) and 3 (1.7%) patients in the sitravatinib+tislelizumab and docetaxel-treated arms, respectively (online supplemental table 4).

Overall, 83 (44.6%) and 66 (37.3%) patients in the sitravatinib+tislelizumab and docetaxel arms, respectively, had serious TEAEs (online supplemental tables 2 and 5). The most common serious TEAEs in the sitravatinib+tislelizumab were pneumonia (16 (8.6%)), death (6 (3.2%)), and haemoptysis (5 (2.7%)) whereas those in the docetaxel arm were pneumonia (17 (9.6%)), neutropenia (8 (4.5%)), neutrophil count decreased (8 (4.5%)), white blood cell count decreased (8 (4.5%)), febrile neutropenia (7 (4.0%)) and pleural effusion (6 (3.4%)) (online supplemental table 5). Of patients experiencing serious haemoptysis, 4 (2.2%) and 0 patients in the sitravatinib+tislelizumab and docetaxel arms, respectively, had events assessed by the investigator as being

Table 3 Treatment-emergent adverse events with an incidence ≥10% (safety analysis set)

Preferred term	Sitravatinib+tislelizumab (n=186)		Docetaxel (n=177)	
	Any grade n (%)	≥Grade 3 n (%)	Any grade n (%)	≥Grade 3 n (%)
Patients with ≥1 TEAE with incidence ≥10%	183 (98.4)	121 (65.1)	162 (91.5)	100 (56.5)
Aspartate aminotransferase increased	111 (59.7)	6 (3.2)	18 (10.2)	3 (1.7)
Alanine aminotransferase increased	97 (52.2)	5 (2.7)	17 (9.6)	4 (2.3)
Diarrhoea	83 (44.6)	9 (4.8)	26 (14.7)	5 (2.8)
Blood creatine phosphokinase MB increased	74 (39.8)	5 (2.7)	3 (1.7)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	68 (36.6)	12 (6.5)	0 (0.0)	0 (0.0)
Anaemia	61 (32.8)	7 (3.8)	84 (47.5)	5 (2.8)
Hypoalbuminaemia	58 (31.2)	1 (0.5)	41 (23.2)	0 (0.0)
Hypertension	56 (30.1)	25 (13.4)	6 (3.4)	2 (1.1)
Weight decreased	54 (29.0)	8 (4.3)	15 (8.5)	1 (0.6)
Decreased appetite	53 (28.5)	2 (1.1)	29 (16.4)	2 (1.1)
Hypothyroidism	46 (24.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatraemia	45 (24.2)	9 (4.8)	18 (10.2)	2 (1.1)
Blood lactate dehydrogenase increased	41 (22.0)	0 (0.0)	8 (4.5)	0 (0.0)
Platelet count decreased	38 (20.4)	8 (4.3)	22 (12.4)	3 (1.7)
Hypokalaemia	36 (19.4)	10 (5.4)	15 (8.5)	4 (2.3)
Proteinuria	34 (18.3)	0 (0.0)	13 (7.3)	0 (0.0)
Rash	32 (17.2)	1 (0.5)	10 (5.6)	0 (0.0)
Vomiting	31 (16.7)	0 (0.0)	19 (10.7)	0 (0.0)
Constipation	30 (16.1)	0 (0.0)	26 (14.7)	0 (0.0)
Haemoptysis	29 (15.6)	5 (2.7)	19 (10.7)	1 (0.6)
Nausea	29 (15.6)	0 (0.0)	25 (14.1)	0 (0.0)
Gamma-glutamyltransferase increased	27 (14.5)	5 (2.7)	13 (7.3)	0 (0.0)
Hypocalcaemia	27 (14.5)	0 (0.0)	13 (7.3)	0 (0.0)
Blood alkaline phosphatase increased	26 (14.0)	1 (0.5)	10 (5.6)	1 (0.6)
Cough	26 (14.0)	0 (0.0)	28 (15.8)	0 (0.0)
Pneumonia	26 (14.0)	17 (9.1)	25 (14.1)	15 (8.5)
Dysphonia	25 (13.4)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatine phosphokinase increased	24 (12.9)	2 (1.1)	6 (3.4)	0 (0.0)
SARS-CoV-2 test positive	23 (12.4)	1 (0.5)	10 (5.6)	0 (0.0)
Blood creatinine increased	20 (10.8)	0 (0.0)	8 (4.5)	0 (0.0)
Blood thyroid stimulating hormone increased	20 (10.8)	0 (0.0)	1 (0.6)	0 (0.0)
Fatigue	20 (10.8)	4 (2.2)	17 (9.6)	0 (0.0)
Insomnia	20 (10.8)	1 (0.5)	14 (7.9)	0 (0.0)
Abdominal pain upper	19 (10.2)	2 (1.1)	3 (1.7)	0 (0.0)
Hypertriglyceridaemia	19 (10.2)	5 (2.7)	5 (2.8)	1 (0.6)
Hyperuricaemia	19 (10.2)	0 (0.0)	8 (4.5)	0 (0.0)
Fever	19 (10.2)	0 (0.0)	12 (6.8)	1 (0.6)
Hyperglycaemia	15 (8.1)	0 (0.0)	18 (10.2)	0 (0.0)
White blood cell count decreased	11 (5.9)	0 (0.0)	66 (37.3)	52 (29.4)
Neutrophil count decreased	10 (5.4)	1 (0.5)	59 (33.3)	51 (28.8)
Lymphocyte count decreased	9 (4.8)	4 (2.2)	19 (10.7)	5 (2.8)
Alopecia	5 (2.7)	0 (0.0)	59 (33.3)	0 (0.0)

Adverse events were classified based on MedDRA V.25.0.
Adverse event grades were evaluated based on NCI-CTCAE V.5.0.
Patients with multiple events for a given preferred term were counted only once at the worst severity for each preferred term.
Events were sorted by decreasing frequency of preferred term in the sitravatinib+tislelizumab any grade group.
MB, muscle-bound; MedDRA, Medical Dictionary for Regulatory Activity; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

related to study treatment (online supplemental tables 6 and 7).

TEAEs leading to death were more common in the sitravatinib+tislelizumab compared with the docetaxel arm (15 (8.1%) vs 5 (2.8%) patients); the most common in the sitravatinib+tislelizumab arm were: unexplained death (4 patients (2.2%) vs 1 (0.6%)), hemoptysis (3 (1.6%) vs 0%), and pneumonia (3 (1.6%) vs 2 (1.1%)) (online supplemental table 8). All other TEAEs leading to death occurred in one patient each in either treatment arm or in both arms (pneumonitis) (online supplemental table 8). The Independent Data Monitoring Committee reviewed and concluded that the fatal haemoptysis events were confounded by squamous central NSCLC in two patients and pre-existing haemoptysis at baseline in one patient. Serious TRAEs and TRAEs leading to death are shown in online supplemental tables 6 and 8, respectively.

SAFFRON301 was terminated due to an imbalanced rate of serious or fatal pulmonary haemorrhage and an unfavourable overall risk–benefit assessment in the sitravatinib+tislelizumab arm.

DISCUSSION

Patients with advanced NSCLC who progress following chemotherapy and/or checkpoint inhibitor-based immunotherapy targeting PD-1/PD-L1 have limited efficacious treatment options.[10] Combining checkpoint inhibitors with agents that target molecular and cellular mechanisms of resistance to checkpoint inhibitors is a rational approach to overcoming resistance.[18] The SAFFRON-301 investigated whether sitravatinib plus tislelizumab can help to overcome resistance to anti-PD-(L)1 agents and improve the clinical outcomes in patients with metastatic or unresectable locally advanced NSCLC who had disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody. At median follow-up times for OS of 11.7 months (sitravatinib+tislelizumab) and 11.4 months (docetaxel), there was no clear OS advantage favouring sitravatinib+tislelizumab over docetaxel. Due to early termination of the study, the number of OS events (171) did not reach the predefined threshold for interim analysis (197); thus, the OS data were immature. IRC-assessed and investigator-assessed PFS were numerically longer with sitravatinib+tislelizumab combination therapy compared with docetaxel, with HRs of 0.82 and 0.64, respectively. While both PFS assessments are exploratory due to the early termination of the study, the investigator-assessed result appears more favourable, which may be a potential bias in open-label trials.

SAFFRON-301 was terminated prematurely due to an unfavourable risk–benefit assessment. There was a numerical imbalance of both serious and fatal haemoptysis between the sitravatinib+tislelizumab and docetaxel arms (serious: n=5 (2.7%) vs n=1 (0.6%), fatal: n=3 (1.6%) vs 0%, respectively). Thus, pulmonary haemorrhage was identified as an important risk of sitravatinib when used in combination with tislelizumab, especially in this population of patients with locally advanced or metastatic squamous and non-squamous NSCLC.

The reasons for an increased risk of pulmonary haemorrhage with sitravatinib+tislelizumab in SAFFRON-301 are unclear. A risk of fatal haemoptysis was not previously identified in SAFFRON-103, a phase Ib study of sitravatinib+tislelizumab in locally advanced/metastatic squamous and non-squamous NSCLC, although treatment-related haemoptysis leading to study drug discontinuation was reported in 2 of 122 (1.6%) patients in the combination therapy arm.[34] Patients with NSCLC are at increased risk of pulmonary haemorrhage due to the disease pathogenesis itself.[39] In a retrospective analysis of patients with lung cancer (n=877), massive and fatal haemoptysis occurred in 29 (3.3%) patients; this was significantly associated with cavitation, squamous histology and bronchial tumours. Non-lethal haemorrhage occurring in 140 patients (15.9%) was not cell-type specific.[40] In SAFFRON-301, a higher percentage of patients who were randomised to the docetaxel arm never received their assigned treatment compared with the sitravatinib+tislelizumab arm (6.8% vs 0.5%). As patients who did not receive study treatment had a very limited follow-up time in the survival analysis, the study results should be interpreted with caution in view of this imbalance observed between treatment arms.

Published literature indicates that histology may play a role in serious/fatal bleeding events. However, because squamous tumours tend to be cavitated and centrally located, it is unclear if histology is an independent risk factor for serious haemorrhage or is a surrogate marker.[39 41] Of the five serious or fatal TEAEs of haemoptysis cases in the sitravatinib+tislelizumab arm in SAFFRON-301, 3 patients had squamous disease, and the other 2 patients had non-squamous histology. Notably, the current study had a higher proportion of patients with squamous histology (51%) compared with similar trials, such as LEAP-008 (27% in lenvatinib+pembrolizumab arm, 31% in docetaxel arm), CONTACT-01 (26% in atezolizumab+cabozantinib arm, 24% in docetaxel arm), and SAPPHIRE (0%).[24 25 42] Based on available data, no definitive conclusion can be made regarding a potential role of histology in the serious/fatal pulmonary haemorrhage events observed in SAFFRON-301 in the sitravatinib+tislelizumab arm. Because the primary tumour location (central or peripheral) was not prospectively collected in this study, we were not able to analyse if the tumour location contributed to the increased occurrence of haemoptysis in sitravatinib+tislelizumab; this is a key limitation of the study.

There are limited data regarding the safety risk of pulmonary haemorrhage in patients treated with multikinase inhibitors. However, the use of bevacizumab and other anti-VEGF agents in some groups of patients with NSCLC resulted in clinically significant or fatal pulmonary haemorrhage.[39] In AVF0757g, a phase II trial of bevacizumab plus carboplatin/paclitaxel in patients with NSCLC, 9% of bevacizumab-treated patients experienced life-threatening pulmonary haemorrhage; squamous cell

histology, tumour necrosis and cavitation, and disease location close to major blood vessels were associated with major haemoptysis.[41] A meta-analysis of randomised controlled trials revealed that unlike ramucirumab, bevacizumab significantly increased the risk of all-grade and high-grade pulmonary haemorrhage in patients with lung cancer.[43] In REVEL, the incidence of overall/≥grade 3 pulmonary haemorrhage was 7%/1% and 6%/1% among patients treated with ramucirumab plus docetaxel and placebo plus docetaxel, respectively, in patients with non-squamous NSCLC compared with 10%/2% and 12%/2% in patients with squamous histology.[44] In LEAP-008, where NSCLC patients were enrolled from a very similar treatment setting to SAFFRON-301, treatment-related fatal haemoptysis was reported for 2/181 patients who received lenvatinib+pembrolizumab, and for 1/47 patients who received lenvatinib monotherapy; no fatal haemoptysis was reported from the docetaxel arm in the same trial.[24]

The lack of an OS benefit with combination therapy in SAFFRON-301 is consistent with the phase III LEAP-008, CONTACT-01 and SAPPHIRE trials where addition of a TKI to a PD-(L)1 inhibitor failed to meet the primary endpoint of improved OS compared with docetaxel in patients with advanced NSCLC that progressed on or after a PD-(L)1 inhibitor and platinum-containing chemotherapy; however, cross-trial comparisons should be cautiously interpreted.[24 25 42] Moreover, the current data strongly suggest that alternative treatment strategies to that of combining a TKI with a PD-(L)1 inhibitor should be considered. Resistance to checkpoint inhibitors is a complex, multimechanism process. In addition to the immunosuppressive tumour microenvironment and TAM receptor activation, coinhibitory checkpoints, defects in antigen processing or neoantigen loss, oncogenic signalling pathways and tumour-mediated immune suppression all contribute to resistance.[45 46] Treatments with novel and diverse mechanisms of action as well as customised therapies are likely needed to overcome resistance to PD-L(1) based therapy in patients with NSCLC who were previously treated with checkpoint inhibitors with or without platinum-based chemotherapy.

In summary, an unclear efficacy benefit in combination with an increased risk of serious and fatal pulmonary haemorrhage in the combination therapy arm led to early termination of SAFFRON-301. As such, the efficacy data should be interpreted with caution due to early termination and thus immature survival data. These efficacy data are, however, consistent with the lack of survival benefit in other phase III trials of addition of a TKI to a PD-(L)1 inhibitor.

Author affiliations
[1]Guangdong Lung Cancer Institute, Guangzhou, Guangdong, China
[2]Guangdong Academy of Medical Sciences, Guangdong Provincial People's Hospital, Guangzhou, Guangdong, China
[3]Southern Medical University, Guangzhou, Guangdong, China
[4]Blacktown Cancer and Haematology Centre, Blacktown, New South Wales, Australia
[5]Department of Respiratory Medicine, Shanghai Geriatric Medical Center, Zhongshan Hospital, Fudan University, Shanghai, China
[6]Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Oncology, Peking University Cancer Hospital and Institute, Beijing, China
[7]Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Beijing, China
[8]Division of Medical Oncology, James Cancer Hospital, Pelotonia Institute for Immuno-Oncology, The Ohio State University, Columbus, Ohio, USA
[9]Department of Respiratory Medicine, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[10]Department of Lung Internal Medicine, Xinjiang Cancer Hospital, Urumqi, Xinjiang, China
[11]Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
[12]Department of Respiratory, Shandong Cancer Hospital, Jinan, Shandong, China
[13]Pindara Private Hospital, Benowa, Queensland, Australia
[14]Cancer Research South Australia, Adelaide, South Australia, Australia
[15]BeOne Medicines Ltd. (Beijing) Co., Ltd, Beijing, China
[16]BeOne Medicines, Beijing, China
[17]Guangdong Provincial People's Hospital Guangdong Lung Cancer Research Institute, Guangzhou, Guangdong, China

Acknowledgements We would like to thank the investigators, site support staff and especially the patients for participating in this study. We thank Fan Yu and Xin (Cindy) Li (formerly of BeOne Medicines) for their contributions to the study. Medical writing support, under the direction of the authors, was provided by Lori Kornberg, PhD, and Smitha Reddy, PhD, of Envision Pharma, and was funded by BeOne Medicines.

Contributors QZ, BG, JH, JZhao, MW, KH and Y-LW contributed to study conception and/or design. QZ, WZheng, CW, YC, JZhang, JW and Y-LW contributed to data interpretation. WZheng, CW, YC, JZhang and JW contributed to data analysis. QZ, BG, JH, JZhao, MW, WZhang, CL, JF, XyL, ZW, MM, VK, JZhang and JW contributed to data acquisition. CW is the guarantor. All authors contributed to drafting the manuscript or participated in revising it critically for important intellectual content, provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors accepted responsibility to submit for publication.

Funding BeOne Medicines funded the study, obtained the regulatory and ethics approvals, developed the trial protocol, provided study drugs, collected and analysed the data, and funded medical writing. The authors assisted with data collection, analysis and interpretation. BeOne Medicines and the authors approved the final version of the manuscript for submission.

Competing interests QZ: Received honoraria from: AstraZeneca, Lilly, Roche, Pfizer, Boehringer Ingelheim, MSD Oncology, Bristol Myers Squibb, Hengrui outside the submitted work. BG: Nothing to disclose. JH: Nothing to disclose. JZhao: Nothing to disclose. MW: Nothing to disclose. KH: Held a consulting or advisory role with: Perthera, Mirati Therapeutics, Bristol Myers Squibb, Iovance Biotherapeutics, Lyell Immunopharma, AstraZeneca, Obsidian Therapeutics, BioNTech SE, Pfizer, Oncoc4; Received research funding to his institution from: Bristol Myers Squibb, Mirati Therapeutics, Adaptimmune, Genentech/Roche, GlaxoSmithKline, Amgen, Iovance Biotherapeutics, AbbVie, Oncoc4. WZhang: Nothing to disclose. CL: Nothing to disclose. JF: Nothing to disclose. XyL: Nothing to disclose. ZW: Nothing to disclose. MM: Nothing to disclose. VK: Nothing to disclose. WZheng, CW, JZhang and JW are employed by BeOne Medicines and may hold stock or other ownership. YC was employed by BeOne Medicines at the time that this study was conducted and may hold stock or other ownership. Y-LW: Received honoraria from: AstraZeneca, BeOne Medicines, Eli Lilly, Hengrui, Pfizer, Roche and Sanofi; held a consulting or advisory role with: AstraZeneca, Boehringer Ingelheim and Roche outside the submitted work; received research funding from: AstraZeneca, Pfizer.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The protocol, protocol amendments and informed consent forms were reviewed and approved by the Independent Ethics Committee (IEC)/Institutional Review Board in conformance with Good Clinical Practice (GCP) and applicable regulatory requirements at each study site. This study was conducted in accordance with the principles of GCP, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, the

Declaration of Helsinki and applicable local regulatory requirements. All participants or legally authorised representatives provided informed consent prior to screening procedures.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. On request, and subject to certain criteria, conditions and exceptions, BeOne Medicines will provide access to individual deidentified participant data from applicable BeOne Medicines-sponsored studies. BeOne Medicines shares data only when permitted by applicable data privacy and security laws and regulations, shares when it is feasible to do so without compromising the privacy of the study participants, and other considerations. Data requests may be submitted to ClinicalTrials@beonemed.com.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Qing Zhou https://orcid.org/0000-0002-0478-176X
Mengzhao Wang https://orcid.org/0000-0002-9226-5393
Jian Fang https://orcid.org/0000-0003-3697-4563
Yi-Long Wu https://orcid.org/0000-0002-3611-0258

REFERENCES

1 Hendriks LE, Kerr KM, Menis J, *et al*. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34:358–76.
2 Riely GJ, Wood DE, Ettinger DS, *et al*. Non–Small Cell Lung Cancer, Version 4.2024. *J Natl Compr Canc Netw* 2024;22:249–74.
3 Singh N, Temin S, Baker S, *et al*. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline. *J Clin Oncol* 2022;40:3323–43.
4 Gandhi L, Rodríguez-Abreu D, Gadgeel S, *et al*. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;378:2078–92.
5 Paz-Ares L, Luft A, Vicente D, *et al*. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. *N Engl J Med* 2018;379:2040–51.
6 Paz-Ares LG, Ramalingam SS, Ciuleanu T-E, *et al*. First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial. *J Thorac Oncol* 2022;17:289–308.
7 Socinski MA, Jotte RM, Cappuzzo F, *et al*. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* 2018;378:2288–301.
8 West H, McCleod M, Hussein M, *et al*. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019;20:924–37.
9 Walsh RJ, Soo RA. Resistance to immune checkpoint inhibitors in non-small cell lung cancer: biomarkers and therapeutic strategies. *Ther Adv Med Oncol* 2020;12:1758835920937902.
10 Moliner L, Spurgeon L, Califano R. Controversies in NSCLC: which second-line strategy after chemo-immunotherapy? *ESMO Open* 2023;8:100879.
11 Crinò L, Mosconi AM, Scagliotti G, *et al*. Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: A phase II trial. *J Clin Oncol* 1999;17:2081–5.
12 Garon EB, Ciuleanu T-E, Arrieta O, *et al*. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014;384:665–73.
13 Gridelli C, Perrone F, Gallo C, *et al*. Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. *Anticancer Res* 1999;19:4535–8.
14 Hanna NH, Kaiser R, Sullivan RN, *et al*. Nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with relapsed or refractory, advanced non-small cell lung cancer (LUME-Lung 2): A randomized, double-blind, phase III trial. *Lung Cancer (Auckl)* 2016;102:65–73.
15 Reck M, Kaiser R, Mellemgaard A, *et al*. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014;15:143–55.
16 Shepherd FA, Dancey J, Ramlau R, *et al*. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–103.
17 Yoneshima Y, Morita S, Ando M, *et al*. Phase 3 Trial Comparing Nanoparticle Albumin-Bound Paclitaxel With Docetaxel for Previously Treated Advanced NSCLC. *J Thorac Oncol* 2021;16:1523–32.
18 Horvath L, Thienpont B, Zhao L, *et al*. Overcoming immunotherapy resistance in non-small cell lung cancer (NSCLC) - novel approaches and future outlook. *Mol Cancer* 2020;19:141.
19 Zhao Y, Guo S, Deng J, *et al*. VEGF/VEGFR-Targeted Therapy and Immunotherapy in Non-small Cell Lung Cancer: Targeting the Tumor Microenvironment. *Int J Biol Sci* 2022;18:3845–58.
20 Du W, Huang H, Sorrelle N, *et al*. Sitravatinib potentiates immune checkpoint blockade in refractory cancer models. *JCI Insight* 2018;3:e124184.
21 Taylor MH, Lee C-H, Makker V, *et al*. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. *J Clin Oncol* 2020;38:1154–63.
22 Neal JW, Santoro A, Viteri S, *et al*. Cabozantinib (C) plus atezolizumab (A) or C alone in patients (pts) with advanced non–small cell lung cancer (aNSCLC) previously treated with an immune checkpoint inhibitor (ICI): Results from Cohorts 7 and 20 of the COSMIC-021 study. *JCO* 2022;40:9005.
22 Reckamp KL, Redman MW, Dragnev KH, *et al*. Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non-Small-Cell Lung Cancer Previously Treated With Immunotherapy-Lung-MAP S1800A. *J Clin Oncol* 2022;40:2295–306.
24 Leighl N, Paz-Ares L, Abreu DR, *et al*. Phase 3 LEAP-008 study of lenvatinib plus pembrolizumab versus docetaxel for metastatic non-small cell lung cancer (NSCLC) that progressed on a PD-(L)1 inhibitor and platinum-containing chemotherapy. *Ann Oncol* 2023;20:100537.
25 Neal J, Pavlakis N, Kim S-W, *et al*. CONTACT-01: A Randomized Phase III Trial of Atezolizumab + Cabozantinib Versus Docetaxel for Metastatic Non-Small Cell Lung Cancer After a Checkpoint Inhibitor and Chemotherapy. *J Clin Oncol* 2024;42:2393–403.
26 National Library of Medicine. ClinicalTrials.gov: ramucirumab plus pembrolizumab vs usual care for treatment of stage IV or recurrent non-small cell lung cancer following immunotherapy, pragmatica-lung study. 2024. Available: https://clinicaltrials.gov/study/NCT05633602 [Accessed 24 Feb 2025].
27 Bauer T, Cho BC, Heist R, *et al*. First-in-human phase 1/1b study to evaluate sitravatinib in patients with advanced solid tumors. *Invest New Drugs* 2022;40:990–1000.
28 Patwardhan PP, Ivy KS, Musi E, *et al*. Significant blockade of multiple receptor tyrosine kinases by MGCD516 (Sitravatinib), a novel small molecule inhibitor, shows potent anti-tumor activity in preclinical models of sarcoma. *Oncotarget* 2016;7:4093–109.
29 Akalu YT, Rothlin CV, Ghosh S. TAM receptor tyrosine kinases as emerging targets of innate immune checkpoint blockade for cancer therapy. *Immunol Rev* 2017;276:165–77.
30 Garton AJ, Seibel S, Lopresti-Morrow L, *et al*. Anti-KIT Monoclonal Antibody Treatment Enhances the Antitumor Activity of Immune Checkpoint Inhibitors by Reversing Tumor-Induced Immunosuppression. *Mol Cancer Ther* 2017;16:671–80.
31 Pircher A, Wolf D, Heidenreich A, *et al*. Synergies of Targeting Tumor Angiogenesis and Immune Checkpoints in Non-Small Cell Lung Cancer and Renal Cell Cancer: From Basic Concepts to Clinical Reality. *Int J Mol Sci* 2017;18:2291.
32 Zhang L, Geng Z, Hao B, *et al*. Tislelizumab: A Modified Anti-tumor Programmed Death Receptor 1 Antibody. *Cancer Control* 2022;29:10732748221111296.
33 Zhang T, Song X, Xu L, *et al*. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. *Cancer Immunol Immunother* 2018;67:1079–90.

34 Zhao J, Yu X, Huang D, *et al*. SAFFRON-103: a phase 1b study of the safety and efficacy of sitravatinib combined with tislelizumab in patients with locally advanced or metastatic non-small cell lung cancer. *J Immunother Cancer* 2023;11:e006055.
35 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
36 U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0. 2017. Available: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [Accessed 24 Feb 2025].
37 Brahmer JR, Lacchetti C, Schneider BJ, *et al*. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *JCO* 2018;36:1714–68.
38 Haanen JBAG, Carbonnel F, Robert C, *et al*. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28:iv119–42.
39 Reck M, Barlesi F, Crinò L, *et al*. Predicting and managing the risk of pulmonary haemorrhage in patients with NSCLC treated with bevacizumab: a consensus report from a panel of experts. *Ann Oncol* 2012;23:1111–20.
40 Miller RR, McGregor DH. Hemorrhage from carcinoma of the lung. *Cancer* 1980;46:200–5.
41 Johnson DH, Fehrenbacher L, Novotny WF, *et al*. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184–91.
42 Borghaei H, de Marinis F, Dumoulin D, *et al*. SAPPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *Ann Oncol* 2024;35:66–76.
43 Xiao B, Wang W, Zhang D. Risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab: a meta-analysis of 85 randomized controlled trials. *Onco Targets Ther* 2018;11:5059–74.
44 Eli Lilly and Company. CYRAMZA - ramucirumab solution. Prescribing information. 2022. Available: https://uspl.lilly.com/cyramza/cyramza.html#section-1 [Accessed 24 Feb 2025].
45 Aldea M, Andre F, Marabelle A, *et al*. Overcoming Resistance to Tumor-Targeted and Immune-Targeted Therapies. *Cancer Discov* 2021;11:874–99.
46 Peters S, Paz-Ares L, Herbst RS, *et al*. Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects. *J Immunother Cancer* 2022;10:e004863.